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Selectivity and lifetime effects in zeolite-catalyzed Baeyer-Villiger oxidation investigated in batch and continuous flow

Keiko Yakabi,^[a] Kirstie Milne,^[a] Antoine Buchard^[b] and Ceri Hammond*^[a]

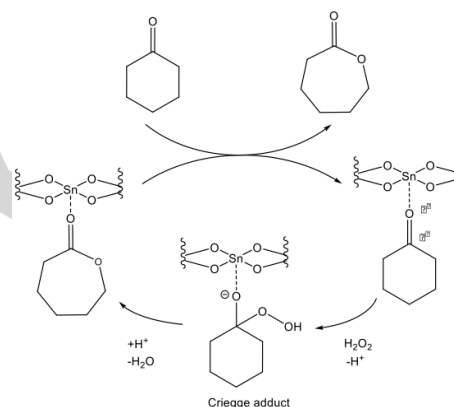
Abstract: In this manuscript, we investigate the kinetic, mechanistic and lifetime aspects of the Baeyer-Villiger oxidation of cyclohexanone with Sn- β as catalyst and H₂O₂ as oxidant, with the aim of 1) elucidating the overall reaction network, 2) closing the carbon balance, particularly at high levels of conversion, and 3) examining the intensification of this process in the continuous regime. The results presented herein conclusively demonstrate that this reaction is highly selective to the desired product (ϵ -caprolactone) only below conversions of 60 %. Above this level of conversion, unavoidable hydrolysis of ϵ -caprolactone to 6-hydroxyhexanoic acid is observed, which consumes the desired product and leads to a reduction in catalytic activity through poisoning. By elucidating the reaction network and working under optimized conditions, we show the potential viability of this methodology to operate continuously over a 180 h period, both at high levels of productivity (324 g (cyclohexanone converted) cm⁻³ (reactor volume) kg⁻¹ (catalyst) h⁻¹) and selectivity (\pm 70 % at 60 % conversion). Over 5000 substrate turnovers were observed during this period, an order of magnitude higher than previously noted for this particular catalyst system.

Introduction

The Baeyer Villiger oxidation (BVO) reaction has been widely studied over the past 100 years, since its discovery in 1899.^[1] It has demonstrated itself to be an especially profitable method to convert ketones, readily available building blocks in organic chemistry, into more complex and valuable esters and lactones.^[2] A key example of this chemistry is the industrially employed BVO of cyclohexanone (CyO), to yield ϵ -caprolactone, a key monomer in the bulk chemical industry.^[3] Traditionally, this chemistry has been performed using peracid-based oxidants, such as mCPBA (*meta*-chloroperbenzoic acid). Unfortunately, such oxidants possess several drawbacks, including the co-production of by-products (carboxylic acids), low active oxygen content, potential explosiveness and a requirement for undesirable chlorinated solvents.^[4] Additionally, they typically demonstrate poor levels of selectivity for oxidation reactions when other functional groups, such as C=C double bonds, are present in the substrate.

To overcome these problems, much effort has been made towards replacing peracid oxidants for greener, less polluting, and potentially less expensive, oxidants.^[5] A key example is

hydrogen peroxide (H₂O₂).^[6] In this case, a suitable catalyst is required to allow H₂O₂ to suitably interact with the ketone substrate. Activation of the oxidant, in addition to the substrate, may therefore be required. Amongst several potential catalytic materials, the Lewis acidic zeolite, Sn- β , has conclusively been shown by Corma *et al.*^[3a] to be the most active, selective, and suitable catalyst for BVO. This material appears to be uniquely able to polarize the carbonyl group of the substrate, thus making it more prone to nucleophilic attack by the oxidant, H₂O₂, without activating the oxidant molecule, thus resulting in high levels of chemoselectivity even when multiple functional groups are present. The most widely accepted mechanism for this reaction is described in Scheme 1.



Scheme 1. Molecular mechanism proposed for the BVO of cyclohexanone catalysed by Sn- β .

Although much work has subsequently been devoted towards to scalable synthesis of Sn- β ,^[7] and the development of novel catalytic processes catalyzed by the same (or similar) material(s), research focusing on the Sn- β catalyzed BVO reaction itself lacks behind, despite the considerable industrial potential. Consequently, several questions and challenges remain. Greatest amongst these are i) the need to identify and optimise all the kinetic parameters of the reaction, ii) the requirement to identify the by-products, and hence close the low carbon balance often observed, and iii) investigate the potential scalability of the system, particularly in the continuous regime. These three challenges constitute the focus of this work.

Results and Discussion

Impact of kinetic parameters. According to our optimized synthesis protocol,^[7a] we prepared a range of Sn- β catalysts from a commercially available Al- β precursor material (SiO₂/Al₂O₃ = 38, from Zeolyst). Sn loadings of 1, 2, 5 and 10 wt. % were achieved by incorporating Sn into the vacant

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framework sites by solid-state incorporation (SSI) with Sn(II)acetate as tin source.

The synthetic and spectroscopic information of these materials was recently extensively described in a detailed manuscript,^[7a] and for brevity will not be shown here. In general, isomorphously-substituted Sn(IV) sites were almost exclusively observed up to a loading of 5 wt. %, although beyond this loading, inactive, extra-framework Sn_xO_y sites were also observed. Accordingly, our primary catalyst, henceforth denoted 2 Sn- β (38)₅₅₀, consisted of 2 wt. % Sn incorporated into the vacant framework sites of zeolite H- β ($\text{SiO}_2/\text{Al}_2\text{O}_3 = 38$) by SSI at 550 °C, as this loading is consistent with a material possessing highly active, isolated Sn(IV) sites.

We first explored the activity of this material for the BVO of CyO under conditions similar to those reported originally by Corma *et al.*^[3a] However, reaction temperatures of 100 °C (internal temperature) were employed, instead of 90 °C. Under the chosen reaction conditions, 2Sn- β (38)₅₅₀ is a highly active catalyst, converting > 60 % of the CyO reactant in 1 h, and > 90 % in < 6 hours. Initially, the system is highly selective (± 90 %) to caprolactone, demonstrating this to be the primary reaction product. However, a remarkable decrease in caprolactone selectivity and total carbon balance is observed as the conversion increases beyond 60 %. Indeed, caprolactone selectivity and total carbon balance decrease from > 90 % during the first 30 minutes of reaction, to ± 50 % after 6 h of reaction. It is also evident that the catalytic rate rapidly decreases above conversion levels of ± 60 %. According to this kinetic profile, caprolactone yield very quickly reaches ± 40 %, but then stagnates and eventually decreases slightly at the highest levels of conversion. This observation, coupled with the corresponding decrease in carbon balance at elevated conversion, strongly points towards the formation of consecutive by-products throughout the reaction period. No additional products could be detected by GC, which is the most routinely applied analytical technique in this area of research. The identity of these by-products is discussed later in the manuscript.

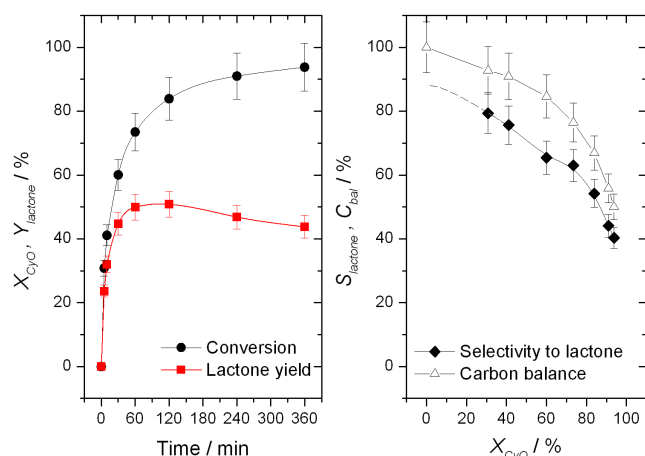


Figure 1. Catalytic activity of 2Sn- β (38)₅₅₀ for the BVO of cyclohexanone. (Left) Conversion and caprolactone yield versus time, and (Right) Selectivity to caprolactone and total carbon balance, both as a function of cyclohexanone conversion.

We subsequently investigated the impact of the Sn loading of the catalyst. In these experiments, various samples of Sn- β , containing between 2, 5 and 10 wt. % of tin, were tested at a fixed amount of Sn relative to cyclohexanone *i.e.* catalyst mass was adjusted so the same amount of Sn was employed in the reactor (1 mol. % relative to CyO). We note here that the theoretical amount of Sn that can be incorporated into dealuminated zeolite ($\text{SiO}_2/\text{Al}_2\text{O}_3 = 38$) is approximately 9 wt. % *i.e.* Sn loadings up to and beyond the theoretical maximum loading were tested. Utilization of high Sn loadings can be beneficial to obtain high space-time yield values and enhance the process profitability. Furthermore, catalysts containing different Sn contents may exhibit different selectivity trends.

As can be seen, reactions performed using the same substrate:metal mole ratio with 2Sn- β and 5Sn- β presented almost identical catalytic activity in terms of conversion (and hence TOF). However, a decrease in activity and TOF was observed as the Sn loading of the catalyst was increased to 10 wt. %. The decrease in activity of this sample (initial (5 min) TOF decreasing from 370 h⁻¹ (2Sn- β) to 199 h⁻¹ (10Sn- β)) indicates that spectator Sn species are present at higher loadings, in agreement to our recent studies of transfer hydrogenation and glucose isomerization over the same materials.^[7] Accordingly, all kinetic parameters were optimized in the presence of 2Sn- β , so as to avoid the potential influence of spectator Sn sites.

At all levels of conversion, each catalyst exhibits comparable selectivity, indicating that the formation of spectator Sn sites does not adversely affect the reaction network, nor catalyze the formation of by-products or consecutive reaction products. Furthermore, the residual Brønsted acid sites from unreacted silanol nests also did not participate in the reaction, indicating that conversion alone determines overall caprolactone selectivity. Accordingly, opportunities to improve selectivity by modifying catalyst composition appear unavailable.

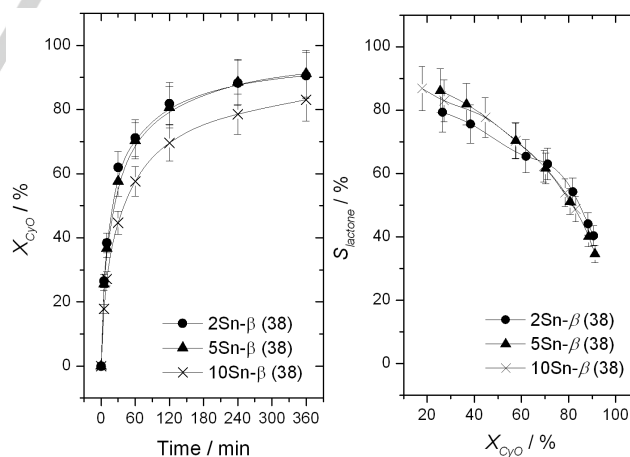


Figure 2. Catalytic activity of various Sn- β samples containing 2-10 wt. % Sn for the BVO of cyclohexanone. (Left) Conversion versus time; (Right) Selectivity to caprolactone as a function of cyclohexanone conversion.

Based on these preliminary results, we subsequently studied the effect of reaction temperature on catalytic activity, selectivity and carbon balance. As the reaction temperature was

decreased from 100 to 40 °C, a clear decrease of CyO conversion was observed. Kinetic analysis of the time online data allowed determination that the catalytic reaction fits better as a second order reaction under the standard conditions (ESI Figure S1), and an activation energy of 51.1 kJ mol⁻¹ was determined. This barrier is comparable to the value reported by Boronat *et al.*^[8] for analogous materials under comparable reaction conditions (45 kJ mol⁻¹).

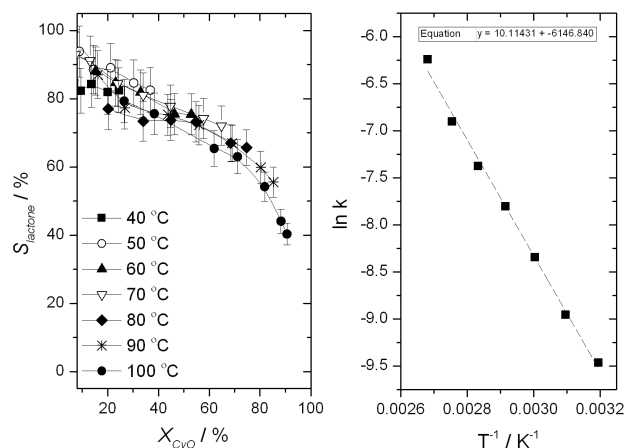


Figure 3. Catalytic activity of 2Sn-β (38)₅₅₀ for the BVO of cyclohexanone at various temperatures. (Left) Conversion versus caprolactone selectivity during BVO of cyclohexanone between 40 and 100 °C; (Right) Arrhenius plot for 2Sn-β (38)₅₅₀ for the BVO of cyclohexanone.

As observed in Figure 3 (Left), regardless of the reaction temperature, high (> 70 %) selectivity to caprolactone was only observed when CyO conversion levels were kept < 50-60 %, after which point selectivity to caprolactone, and total carbon balance, drops noticeably. The selectivity trend is clearly comparable at all reaction temperatures, within experimental error, and selectivity seemingly only depends on the extent of conversion. This indicates that the side reactions or consecutive reactions have comparable activation energies to the BVO reaction, and that high(er) levels of selectivity cannot be obtained through kinetic control.

To determine the effect of H₂O₂ concentration on catalytic rate, a series of experiments with different H₂O₂:ketone ratios were subsequently performed, with all other parameters e.g. Sn content (1 mol. %), reaction temperature (100 °C) and catalyst choice (2Sn-β (38)₅₅₀) remaining unchanged. The initial concentration of hydrogen peroxide was varied from 0.035 to 1M, representing a range of H₂O₂:ketone of ratios 0.1 to 3.0 (under typical conditions, a ratio of 1.5 was employed). The apparent rate constant (k_{app}) at each H₂O₂:ketone ratio was determined at the very initial stages of reaction *i.e.* in the linear region of the kinetic plot, and are represented in Figure 4. Between H₂O₂:ketone ratios of 0.1 and 0.75, a first order dependence on H₂O₂ is observed, with k_{app} increasing linearly with [H₂O₂]. However, above this H₂O₂:ketone ratio, k_{app} reaches a plateau, and the reaction becomes zero order with respect to the oxidant. Once in the zero order regime, excess H₂O₂ does not interfere with the intrinsic kinetics of the system. However, at the highest

oxidant concentration, caprolactone selectivity at all levels of ketone conversion drops somewhat (ESI Figure S2). This indicates that H₂O₂ and/or H₂O (as H₂O₂ is used as an aqueous solution) may be involved in a consecutive reaction that decreases total carbon balance.

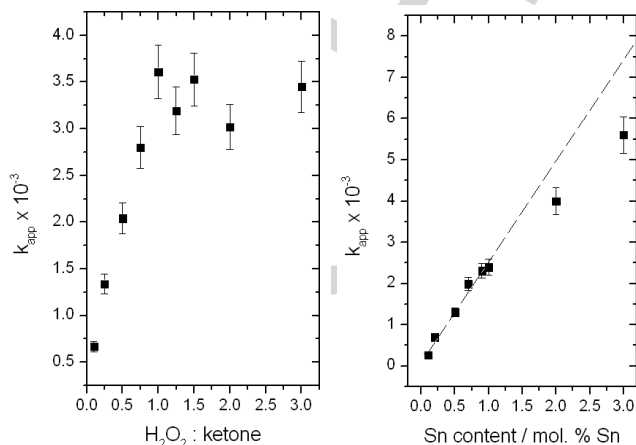


Figure 4. (Left) Effect of [H₂O₂] on the rate of catalytic activity during BVO of CyO at 100 °C, and (Right) Impact of relative Sn content on the rate of BVO at 100 °C.

We subsequently explored the impact of Sn content on the BVO reaction. Under the conditions reported by Corma *et al.*,^[3a] Sn contents of 1 mol. % (relative to CyO) are typically employed. Accordingly, we varied the mass of 2Sn-β (38)₅₅₀ so that Sn contents of 0.1 – 3 mol. % Sn, relative to CyO were utilized. Calculation of k_{app} at all Sn contents was calculated at low conversions, in order to minimize the impact of product induced deactivation. Between 0.1-1 mol. % Sn, a linear relationship between k_{app} and Sn content is observed. However, at very high Sn loadings, k_{app} is lower than anticipated, indicating that some mass transfer limitations are present when large masses of catalyst are used. Accordingly, all further experiments were conducted at Sn contents of 1 mol. % or lower, consistent with the reaction being in the kinetic regime (also evident from the linear Arrhenius plot). In terms of caprolactone selectivity, the trend obtained was maintained throughout all experiments *i.e.* varying the Sn content within the reactor did not overtly impact caprolactone selectivity at any level of conversion.

Identification of by-products and closing the carbon balance. To close the carbon balance, and fully identify the reaction network, we subsequently turned our attention to identifying the nature of the unknown by-products that must be present, accounting for the missing carbon balance. As described above, despite the carbon balance dropping to ca. 60 % at CyO conversions > 70 %, no products other than caprolactone could be detected by GC. From previous studies, the most likely by-products include 6-HHA, formed through caprolactone hydrolysis, and adipic acid, formed *via* the oxidation of 6-HHA.^[9]

We first focused on FTIR spectroscopy, which could be utilized both *ex situ* and *in situ i.e.* inline, in order to allow

identification of the potential C=O species present in the reaction. Although we were able to record the FTIR spectra of three potential reactant species (CyO, caprolactone, 6-HHA and AA, ESI Figure S3), the relative overlap of each C=O signal means that identification of each potential compound in a mixture of all compounds was not feasible (ESI Figure S4).

We subsequently turned our attention to ^1H NMR spectroscopy. Although the presence of the solvent inhibits identification of all potential species within the reaction solution under normal conditions, the relatively high boiling points of CyO and all the potential products allowed us to almost completely evaporate the solvent (1,4-dioxane, boiling point 100 °C) prior to analysis, and consequently obtain satisfactory qualitative data. This immediately revealed the presence of distinct resonances of CyO, caprolactone and 6-HHA in various reaction samples. All ^1H NMR resonances of adipic acid overlap with CyO and 6-HHA (ESI Figures S5 to S8, and hence AA cannot be conclusively identified by ^1H NMR.

Table 1. Caprolactone concentration of various reaction solutions obtained by GC-FID and ^1H -NMR spectroscopy.

Time (min)	[caprolactone] GC-FID ^a	[caprolactone] ^1H -NMR ^b	Standard deviation (%)
0	0	0	0
30	0.132	0.131	0.5
60	0.137	0.132	2.6
120	0.129	0.126	1.7
360	0.098	0.090	6.0

^aDetermined by GC-FID by quantification against biphenyl internal standard;

^bexperimentally determined by ^1H -NMR spectroscopy by quantification against tetramethylsilane.

Quantification of the (by-)products by ^1H NMR was achieved by calibrating a capillary containing a known amount of tetramethylsilane (δ , $\delta = 0.0$ ppm) against known standards (ESI Figure S9). The calibrated capillary was subsequently placed within the NMR tubes of various time online samples of particular reaction solutions, and the concentration of each product in these samples was quantified relative to the calibrated intensity of the TMS signal. To verify this quantification strategy, the caprolactone concentration – obtained by GC-FID analysis against a biphenyl internal standard – was compared to the caprolactone concentration measured by ^1H NMR spectroscopy with calibration against tetramethylsilane. Table 1 demonstrates that the concentration values obtained by this method of quantitative NMR

spectroscopy were within 1-6% of those obtained by GC-FID analysis. We note here that overlapping signals prevents quantification of CyO by this method, and its concentration was solely monitored by GC-FID.

With both GC-FID and ^1H -NMR available, we subsequently repeated the initial BVO of CyO under our standard conditions. With the added quantification of 6-HHA, now quantifiable by ^1H -NMR, the carbon balance of the reaction subsequently improved from 54 % to 88 % at the highest levels of conversion (ESI Table S1). This clearly demonstrates that as conversion increases, selectivity towards 6-HHA increases dramatically, strongly indicating the overall reaction to contain two particular steps: 1) BVO yielding caprolactone, and 2) hydrolysis of caprolactone to 6-HHA.

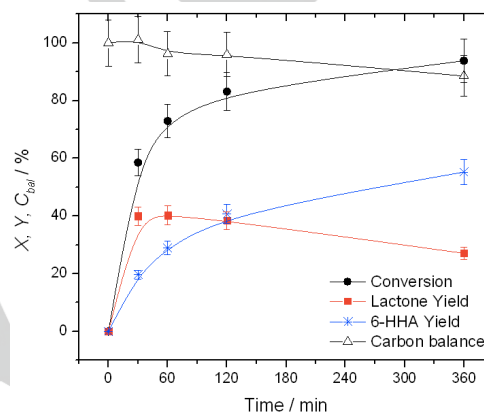


Figure 5. Fully calibrated time online analysis of BVO of CyO at 100 °C, catalyzed by 2Sn-β (38)₅₅₀.

Due to the poor suitability of GC and ^1H NMR to identify and quantify AA, we subsequently utilized ^{13}C NMR and HPLC to investigate the presence of this potential by-product, which may account for the missing carbon balance. Analysis of authentic standards revealed that AA could be separated and quantified by HPLC, and that it possesses a distinct ^{13}C resonance at 175.82 ppm. Although Cavani *et al.*^[10] observed AA as a deep oxidation product during the BVO of CyO with titanium silicalite-1 as catalyst, only trace amounts (< 3 mol. %) of this by-product were observed during the entire reaction period by ^{13}C NMR and HPLC (Figure S10). We attribute the minor amount of this deep oxidation product in this particular to 1) the change in catalyst utilized (titanium silicalite-1 is a catalyst which is known to produce $\bullet\text{OH}$ radicals, which may readily oxidize 6-HHA), and 2) the presence of 1,4-dioxane as solvent, which has been shown to minimize the production of $\bullet\text{OH}$ radicals that lead to AA.

To further close the carbon balance (± 91 % including AA), the spent catalytic materials extracted from the reactor after reaction were also analyzed by Thermogravimetric Analysis (TGA) (ESI Figure S11). The temperature of specific mass losses observed upon heating the *ex reactor* catalyst were compared to those mass losses observed from known standards of CyO, caprolactone, 6-HHA and AA, pre-adsorbed onto a reference 2Sn-β (38)₅₅₀ powder. Thus, TGA of the used catalyst allowed us to determine the type (from the desorption

temperature) and quantity (by the mass loss observed) of adsorbed carbon present on the *ex reactor* catalyst. In addition to some residual solvent, a considerable amount (> 11 % by mass) of caprolactone, and a small amount (3 % by mass) of 6-HHA were detected on the *ex reactor* catalytic material. In total, this corresponded to approximately ± 5 % of the original carbon species introduced into the reaction at the start of the process, and thus raises the carbon balance under the typical BVO conditions to ± 96 %.

We subsequently explored the possible formation of oligomeric and polymeric products, which could readily arise from the polymerization of caprolactone or 6-HHA. Over the first hour of the reaction, no oligomeric products were detected by NMR or Gel Permeation Chromatography (GPC), indicating that polymerization during the early stages of the reaction does not occur. However, at more extended reaction times (2-6 h) and particularly at high levels of conversion, some polymeric products could be observed through ^1H NMR (Figure 6). GPC analysis of these reaction samples revealed these polymeric species to be oligomers of caprolactone, possessing between 2 and 3 caprolactone units (ESI Figure S12). This clearly suggests that performing the reaction continuously at high conversion should be avoided, so as to minimize the opportunity of fouling by oligomer formation. It is likely that the degree of caprolactone oligomerisation fully closes the carbon balance at high levels of conversion, although precise quantification of oligomeric products is not possible at this stage.

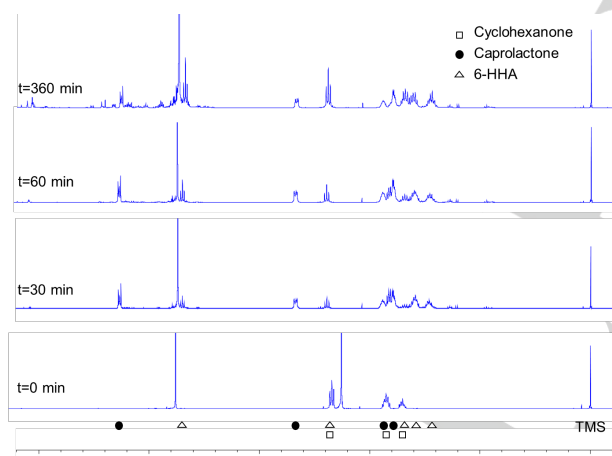


Figure 6. Time online analysis of BVO of CyO at 100 °C by ^1H NMR.

Caprolactone conversion studies. In an attempt to improve the overall caprolactone selectivity levels – particularly at high levels of conversion – we subsequently investigated the caprolactone hydrolysis reaction, responsible for the co-production of 6-HHA. Although dehydration of 6-HHA to caprolactone could be performed in a second step, obtaining high caprolactone selectivity would lead to improved efficiency and minimize downstream processing.

We first investigated the role of the catalyst in the hydrolysis reaction. To do this, a solution of caprolactone in 1,4-dioxane (0.2 M) was placed in a round bottomed flask under the standard

reaction conditions, and two separate experiments were performed. In the first reaction (Table 3, Entry 1), the typical amount of H_2O only (added by necessity when using 50 wt. % H_2O_2) was added to the vessel. In the second experiment (entry 2), 2Sn- β was also added to the reactor, in addition to H_2O . This control experiment was to verify whether hydrolysis of caprolactone proceeded in an uncatalyzed manner, or whether the heterogeneous material promoted the reaction. In both cases, consumption of caprolactone and formation of 6-HHA were monitored by GC and ^1H NMR, respectively. In the absence of catalyst (Table 3, Entry 1), no conversion of caprolactone was observed. In contrast, in the presence of the catalyst, 25 % conversion of caprolactone to 6-HHA (at > 95 % selectivity) was observed. This strongly indicates that some catalyst functionality (potential Lewis acidity, Brønsted acidity, or defect sites) is required to catalyze the hydrolysis reaction.

Table 2. Extent of caprolactone hydrolysis observed under various reaction conditions.

Entry	Catalyst	H_2O (ml)	Conv (%)
1	-	0.15	0
2	2% Sn- β 38	0.15	25
3	deAl β 38	0.15	1.8
4	5% Sn- β 38	0.15	23
5	10% Sn- β 38	0.15	13
6	2% Sn- β 38	0.3	36
7	deAl β 38	0	1.1
8	2% Sn- β 38	0	8
9	5% Sn- β 38	0	7
10	10% Sn- β 38	0	4
11	2% Sn- β 38 Recalcined	0	4
12	2% Sn- β 38	0.3 (50 wt % H_2O_2)	62

To deduce the nature of the catalyst functionality responsible for the hydrolysis reaction, we subsequently investigated the activity of various samples of Sn- β for the hydrolysis reaction alone. In the absence of Sn (Entry 3), dealuminated zeolite β demonstrates extremely low reactivity for the hydrolysis reaction, indicating that defect sites and residual Brønsted acid sites of the zeolite framework alone are not responsible for caprolactone hydrolysis. In contrast, Sn- β (possessing between 2 and 10 wt. % Sn, entries 2, 4 and 5) demonstrates substantial activity for hydrolysis, with up to 25 % conversion being observed over a four hour reaction period. Interestingly, the relative activities of 2, 5 and 10Sn- β samples for caprolactone hydrolysis is identical to the relative activities observed with these samples for the BVO reaction itself (Figure 2). Unfortunately, this strongly indicates that the same Sn sites required for BVO are responsible for caprolactone hydrolysis. Thus, catalyst modification methodologies are unlikely to be able to remove the hydrolysis

side reaction, and 6-HHA formation is likely unavoidable under these reaction conditions. Quantification using the tetramethylsilane capillary confirmed 6-HHA as the main product with a selectivity > 90 % in all of these cases, though trace amounts of oligomers could also be observed at extended reaction periods (ESI Figure S13). Surprisingly, even in the absence of additional water, conversion up to 8 % of caprolactone to 6-HHA was still observed when using different Sn- β catalysts (entries 7 to 10). We subsequently repeated this series of experiments, utilizing freshly calcined Sn- β as opposed to Sn- β that had been stored at ambient conditions for approximately 4-7 days (Entry 11). Though caprolactone conversion was reduced cases, it was not eliminated completely, showing that even trace amounts of water lead to hydrolysis.

Additionally, we studied the effect of H₂O₂ addition (Entry 12). Whilst higher caprolactone conversion was observed when H₂O₂ is present alongside H₂O (62 % (Entry 12) vs. 36 % (Entry 6)), AA was still not observed by ¹³C NMR (Figure S14), and selectivity to 6-HHA was still > 90 %. Although the total absence of AA is likely due to the low sensitivity of the analytical methodologies *i.e.* its concentration is too low for detection, the high selectivity to 6-HHA observed even in this case strongly indicates that ring opening, and not deep oxidation, remains the dominant consecutive reaction. We hypothesize that the increased rate of ring opening in the presence of H₂O₂ may be due to the lower pH/pKa of the solution, and/or the presence of cationic stabilizers in the H₂O₂ solution, both of which may increase the rate of ring opening. Finally, we investigated the temperature dependence of the hydrolysis reaction catalyzed by Sn- β , obtaining an E_{act} of 37 kJ mol⁻¹ (ESI Figure S18), comparable to that of the BVO reaction. Since the reactions are consecutive, effort should be made to control the extent of conversion, and to use the conversion vs. selectivity relationship to maximize selectivity to caprolactone.

Intensification and catalyst stability in continuous flow.

Having identified the nature of the by-products present during BVO, we investigated the potential of each of the (by-)products to poison the catalyst (product induced poisoning), as this may prohibit continuous operation. Indeed, the large decrease in catalytic rate observed after 1 h of batch reaction (Figure 1) indicates product-induced poisoning being present. Accordingly, we repeated the standard BVO reaction at 100 °C (Figure 1) in the presence of various quantities of the reaction (by-)products (particularly caprolactone, water and 6-HHA; AA was not studied due to its low concentration throughout the reaction period). In each case, the conversion of CyO was used to determine the kinetics of the reaction as a function of the amount of (by-)product added. As seen in Figure 7, each of the products added influences the initial rate of reaction. Although water inhibits the rate by approximately 40 % at a by-product level of 50 mol. %, the total amount of water that can be present during the reaction – accounting for the initial H₂O added and assuming total conversion of H₂O₂ to H₂O - is only 3 mol. % relative to CyO, and at this level water does not strongly influence the catalytic rate observed. The addition of caprolactone also leads to a decrease in initial rate, but only by approximately 20 % even at

relatively high *i.e.* 50 mol. %, concentrations. However, 6-HHA is seen to strongly influence the initial catalytic activity, as the initial rate of Sn- β is found to decrease by approximately 50 % when 50 mol. % 6-HHA, relative to CyO, is added, although less amounts of 6-HHA are not so inhibiting for the rate of reaction. This clearly demonstrates that the continuous reactor should be held at a level of conversion consistent with there being as little 6-HHA present as possible. A conversion level of approximately 50-60 % (corresponding to a 6-HHA level of approximately 15-25 mol. %, and a decrease in rate of \pm 20 %) appears to be a good target. The strong decrease in rate observed at 6-HHA levels of \pm 50 mol. % corresponds well to the decrease in catalytic rate observed in the initial batch experiments at conversion levels of 60 % and above, where 6-HHA begins to become the major reaction product.

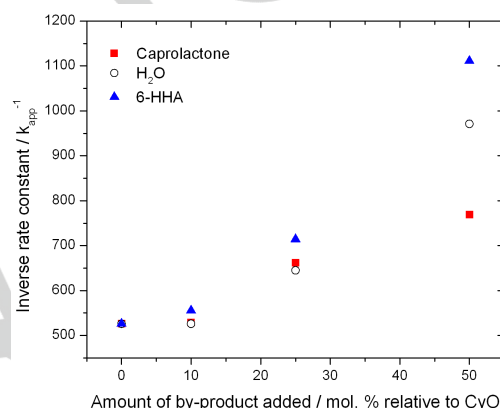


Figure 7. Effect of by-product addition on the initial rate of BVO observed with 2Sn- β (38)₅₅₀. Inverse rate constants were determined by measuring the decrease in CyO concentration as a function of reaction time by GC-FID.

Having deduced the impact of the potential reaction products on reaction rate, we subsequently set about exploring the activity of this system in continuous flow. A continuous Plug Flow Reactor (PFR) offers major advantages over a slurry reactor, including i) improved process control and safety, ii) excellent mass- and heat-transfer, iii) shorter reaction times, iv) smaller reactor volumes, iv) scalability and v) increased space-time-yields. In addition, continuous PFRs allow critical evaluation of a catalysts stability and lifetime under steady state conditions. The reactor employed was adapted from a kinetically relevant PFR optimized for the Sn- β catalysed isomerization of glucose to fructose^[11] and the transfer hydrogenation of carbonyl compounds.^[12] Kinetic relevance of the reactor for BVO was also fully benchmarked (ESI Figure S19), with testing being performed in the absence of external mass transfer limitations.

According to the product induced-deactivation studies above (Figure 7), we targeted contact times that would lead to a conversion level of approximately 60 %, so as to minimize the influence of 6-HHA on catalyst lifetime (Figure S19). In our initial reaction, a H₂O₂:ketone ratio of 1.5 was employed, consistent with typical batch experiments. As can be seen (Figure 8, Left, blue triangles), apart from a very short induction period, catalytic activity remains relatively constant over a period of 180 h, with a

steady state CyO conversion of $\pm 60\%$ being observed. No major modifications in selectivity were observed upon moving into the continuous reactor, and the conversion versus caprolactone selectivity trend sits on the same profile as found for the batch reactor at the same H_2O_2 :ketone ratio (Figure 8, right).

Clearly, the $\text{Sn-}\beta/\text{H}_2\text{O}_2$ BVO system possesses tremendous levels of stability. Over the course of 180 h, the catalyst performed > 5000 substrate turnovers,^[13] equivalent to over 50 complete batch reactions. Notably, the TON values observed are an order of magnitude higher than previously observed for the same catalytic system.^[3a] Only negligible changes in steady state activity were observed during this period, even without periodic regeneration being performed. Re-calcination of the catalyst bed after 180 h nevertheless restores initial activity, demonstrating that the slight change in activity is reversible, further demonstrating the excellent stability of this system.

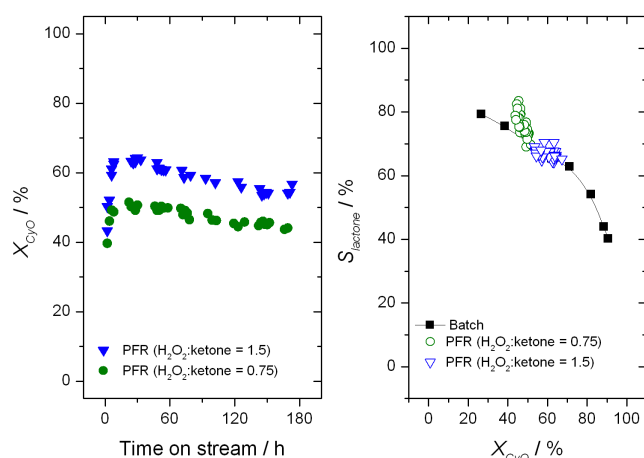


Figure 8. (Left) Conversion versus time on stream during BVO of CyO in the continuous regime at 100 °C, and (Right) selectivity to caprolactone observed at different degrees of CyO conversion in both batch and continuous mode.

Table 3. Relative performance of $\text{Sn-}\beta$ for BVO chemistry in batch and flow.

Reactor type	Space-time-yield ^a	Relative space-time-yield	Lactone selectivity @ max. STY (%)
batch ^b	24.5	1	39
flow ^c	323.9	13.2	70

Space-time-yields were calculated at maximum conversion as g of reactant converted per cm^3 reactor volume, per hour and per kg of catalyst. ^bOnly the liquid volume was used as reactor volume. ^cVolume of catalyst bed (including diluent) used as reactor volume.

In addition to excellent stability, performing the reaction in plug flow mode also leads to tremendous improvements in the productivity of the system, even at the same reaction

temperatures used for the batch experiments. Space-time-yield at 100 °C in the continuous reactor increases by one order of magnitude relative to the batch reactor system.^[14] Notably, the caprolactone selectivity obtained at the maximum STY of each reactor is also substantially higher in the PFR (70 vs. 39 %), although as a function of conversion no substantial improvements are observed at the same H_2O_2 :ketone ratio.

Finally, we explored the potential of the system to operate in an oxidant-limited regime. From the batch studies (Figure 4, Left), it was shown that almost identical catalytic rates were observed at a H_2O_2 :ketone ratio of 0.75 as were observed at the typical 1.5 ratio *i.e.* the BVO reaction is zero order in $[\text{H}_2\text{O}_2]$ above this level. Although operating in an oxidant-limited regime would limit the system to $< 75\%$ CyO conversion, the target level of conversion (50–60 %) would still be achievable, and the decrease in water may limit the caprolactone hydrolysis reaction. We subsequently repeated the continuous experiment at the lower H_2O_2 :ketone ratio of 0.75, keeping all other experimental parameters, including temperature, flow rate, catalyst mass, and reactor volume, identical. In good agreement to the initial PFR experiment, excellent stability is observed in the oxidant limited regime, although CyO conversion was approximately 10 % lower across the entire time period. In terms of activity, the maximum conversion obtained was 51 %, dropping to 44 % after 180 h. Clearly, decreasing the amount of H_2O does not overly impact catalyst stability, in good agreement to the product-induced deactivation studies (Figure 7).

However, decreasing the oxidant concentration does lead to a slight improvement in caprolactone selectivity at all overlapping ketone conversion levels. Indeed, caprolactone selectivity increases to 85 % at a CyO conversion of 40 % in the oxidant-limited regime. However, given the minimum amount of H_2O required for ring opening, it is clear that complete suppression of ring opening under these conditions is unlikely.

Operating with less oxidant also leads to major improvements in the H_2O_2 -based selectivity of the reaction (ESI Figure S20). At a H_2O_2 :ketone ratio of 0.75, a H_2O_2 -based selectivity (*i.e.* moles CyO converted / moles H_2O_2 consumed) of $85 \pm 4\%$ was obtained, clearly indicating that most of the peroxide is used selectively for oxidation. In contrast, a maximum H_2O_2 -based selectivity of only 57 % was obtained when a H_2O_2 :ketone ratio of 1.5 was employed in otherwise identical circumstances. Clearly, decreasing the concentration of H_2O_2 leads to noticeable improvements in H_2O_2 utilization, without overly compromising the BVO process itself. Such improvements are of tremendous importance to both process economics and the sustainability of the reaction, particularly given the cost of H_2O_2 .

Conclusions

The Baeyer-Villiger oxidation of cyclohexanone by $\text{Sn-}\beta/\text{H}_2\text{O}_2$ was studied in batch and continuous mode, in an attempt to understand the mechanistic aspects of the reaction, and identify its potential scalability. It is demonstrated that the BVO of CyO by $\text{Sn-}\beta/\text{H}_2\text{O}_2$ is a challenging reaction, and that

consecutive reactions – particularly the hydrolysis of the primary caprolactone product – can substantially decrease the efficiency (selectivity) and activity (rate) of the process. Largely, this is due to the unavoidable formation of 6-hydroxyhexanoic acid (6-HHA) by caprolactone hydrolysis, which leads to partial poisoning of the Sn- β catalyst, and also consumes the desired caprolactone product, decreasing carbon-based selectivity. Optimizing the reaction conditions so as to minimize 6-HHA formation nevertheless shows the potential scalability of this system in the continuous regime. Operating the reaction at conversion levels < 60 %, at which point 6-HHA formation is less pronounced, results in a stable catalytic system that operates for 180 h without major loss in activity, yielding a turnover number > 5000, and a volumetric productivity of 324 g (ketone converted) cm⁻³ (reactor volume) g⁻¹ (catalyst) h⁻¹. In addition to being one order of magnitude more productive on a space-time-yield basis, the continuous system is also more selective to caprolactone at these elevated productivities (70 % vs. 39 %), and more selective with the H₂O₂ utilized, thus demonstrating the major advantages of the continuous system.

Experimental Section

Catalyst synthesis and pre-treatment. Zeolite Al- β (Zeolyst, NH₄-form, SiO₂/Al₂O₃ = 38) was dealuminated by treatment in HNO₃ solution (13 M HNO₃, 100 °C, 20 h, 20 mL g⁻¹ zeolite). The dealuminated powder was washed with water and dried overnight at 110 °C. Solid-state stannation was performed by grinding the appropriate amount of tin (II) acetate with the necessary amount of dealuminated zeolite for 10 minutes in a pestle and mortar, prior to heat treatment in a combustion furnace (Carbolite MTF12/38/400). A two stage heat treatment was employed: to 550 °C (10 °C min⁻¹ ramp rate) first in a flow of N₂ (3 h not including ramp period) and subsequently air (3 h) for a total of 6 h plus heating and cooling periods. Gas flow rates of 60 mL min⁻¹ were employed at all times. The sample was held horizontally in an alumina combustion boat (10 mL capacity), and a quartz tube was used to seal the sample environment.

Kinetic evaluation and analytical methods. Batch BVO reactions were performed in a 100 mL round bottom flask equipped with a water-free reflux condenser. Reaction temperature was controlled by immersion in a silicon oil bath. The vessel was charged with a 10 mL solution of cyclohexanone in 1,4-dioxane (0.33 M), which also contained an internal standard (biphenyl, 0.01M), and the appropriate amount of catalyst. The vessel was subsequently heated to the desired temperature (100 °C internal temperature). The reaction was initiated by addition of an appropriate amount of H₂O₂, typically corresponding to a H₂O₂:ketone ratio of 1.5. The solution was stirred at \pm 750 rpm with an oval magnetic stirrer bar. Aliquots of reaction solution were taken periodically for analysis, and were centrifuged prior to injection into a GC (Agilent 7820, 25m CP-Wax 52 CB). Reactants were quantified against a biphenyl internal standard. H₂O₂ concentrations were determined by titration against Ce⁴⁺. Batch caprolactone hydrolysis reactions were performed following the same procedure and reaction

conditions as used for the BVO reaction, although cyclohexanone was replaced with caprolactone.

Continuous BVO reactions were performed in a home-made plug flow, stainless steel, tubular reactor. Reactant delivery (0.33 M CyO in 1,4-dioxane, H₂O₂:ketone 1.5 or 0.75) was performed by an HPLC pump. The catalyst (0.4 g) was mixed with a diluent material (SiC (particle size of 63-75 μ m), 1.6 g) in order to avoid back mixing and to minimize pressure drop, and the bed placed in between two plugs of quartz wool. The diluted catalyst was densely packed into a 1/4" stainless steel tube (4.1 mm ID), and a frit (0.5 μ m) was placed at the end of the bed in order to avoid any loss of material. A contact time of 9.75 min was typically employed. The reactor temperature was controlled by immersion in a thermostatted oil bath, and pressure was controlled by means of a backpressure regulator. The reaction feed was identical to that used for batch reactions. Aliquots of the BVO reaction solutions were taken periodically from a sampling valve placed after the reactor, and were analyzed in the same manner as the batch reactions.

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Author Contributions. CH designed and guided the research. KY prepared the catalysts, and KY and KM tested the catalysts for under the supervision of CH. Analytical experiments were devised and guided by CH and AB, and were performed by KY. All authors have given approval to the final version of the manuscript.

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Keywords: Zeolites • Tin • Lewis Acids • Baeyer Villiger Oxidation • Continuous flow

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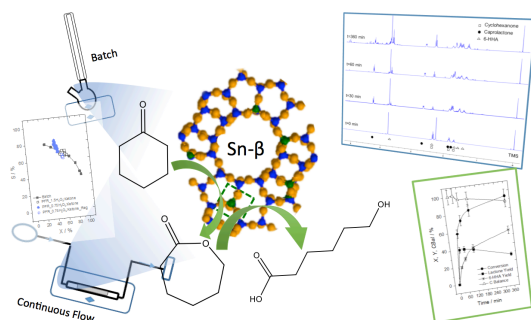
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- 13 Flow rate = 0.16 mL min⁻¹; [CyO] = 0.33 M; Mass (Sn-β) = 400 mg; Sn loading = 2 wt. %. Accordingly, 0.783 moles CyO / mole Sn passes through the column per minute. Over 180 h, this equals approximately 8456.4 turnovers in the column. At a steady-state conversion of 60 % (approximate average over 180 h) this equals approximately 5074 turnovers.
- 14 a) Batch reactor. [CyO] = 0.33 M; volume = 10 mL; Mass of Sn-β = 200 mg; Max conversion = 91 %; Time = 6 h. b) Flow reactor. [CyO] = 0.33 M; Flow rate = 0.16 mL min⁻¹; Reactor volume: 1.56 mL; Mass of Sn-β = 400 mg; Max conversion = 65 %.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

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The mechanistic and intensification aspects of the Baeyer-Villiger oxidation of cyclohexanone to caprolactone is investigated in the batch and continuous regimes.



Keiko Yakabi,^[a]
Kirstie Milne,^[a]
Antoine Buchard,^[b]
Ceri Hammond^[a]

Page No. – Page
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